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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,597	11/21/2003	Natalie C. Twine	31896-012000	3640

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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 12/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/717,597	TWINE ET AL.	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/7/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *14,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/19/05 and all*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (Claims 1-18) in the reply filed on 11/7/2005 is acknowledged. The traversal is on the ground(s) that searches of all the invention groups will not impose a serious burden. This is not found persuasive because the different groups are drawn to different and distinct inventions. Group II is drawn to a kit and requires searches of different components such as different polynucleotides and/or antibodies. Group III is directed to a system and would require searches of computer programs and/or hardwares. These additional searches would impose a serious burden on the office.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 19 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/7/2005.

3. Applicant's election with traverse of the following:

A.) Gene TLR2;

B.) SEQ ID NO. 1;

C.) CPS No. 1 (2325-2635 of SEQ ID NO: 1);

D.) SEQ ID NO: 240.

in the reply filed on 11/7/05 is acknowledged. The traversal is on the ground(s) that the restriction requirement would alter the subject matter of the claimed invention. This is found

persuasive. However, to aid in the prosecution of the case, the above elections would be treated as species selection. Accordingly, Claim 14 (since applicants elected a single gene) and the non-elected species are withdrawn from each corresponding claims.

The species are distinct, each from the other, because their structure and modes of action are different. They would also differ in their reactivity and the starting materials from which they are made. For different species of method, the method steps for each species would differ. Moreover, the above species can be separately classified. Consequently, the species have different issues regarding patentability and represent patentably distinct subject matter. Therefore, this does create an undue search burden, and election for examination purpose as indicated is proper.

4. Claims 1-20 are currently pending;

Claims 14, 19 and 20 have been withdrawn;

Claims 1-13 and 15-18 are being examined in this application.

Priority

5. This application claims priority to provisional applications 60/427,982 filed on 11/21/2003, and 60/459,782 filed on 04/03/2003. The provisional application 60/427,982 does not provide support for Table 6, which would not obtain the benefit of the priority date (11/21/2003) of the provisional application.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1, 2, 4-7, 9, 10 and 16-18 are rejected under **35 U.S.C. 102(b)** as being anticipated by Ralph et al (US 6,190,857 B1; 2/20/2001).

The instant claims briefly recite a method comprising comparing gene expression profiles of one or more genes from peripheral blood cell samples (peripheral blood mononuclear cells) between patents with a solid tumor and disease-free humans. If the one or more genes consist of only one gene, then it could not be IL1B, IL6, MMP-9 or FCGR3B. If the one or more genes consist of two genes, then the combination could not be IL1B and IL6. The solid tumor disease could be RCC (renal cell carcinomas), prostate cancer, OR head/neck cancer.

Ralph et al teach diagnostic techniques for the detection of human disease states that affect gene expression in peripheral leukocytes (which would read on peripheral blood mononuclear cells; See Abstract). The reference teaches a method of detecting prostate cancer in a biological sample (would read on solid tumor disease) comprising measuring the levels of IL-8 or IL-10 in combination with at least one prostate disease marker in said sample (would read on one or more genes in said peripheral blood sample). (See Claim 1) The reference also teaches the method further comprises of comparing the gene levels with corresponding levels obtained

from reference populations of normal individuals (would read on comparing expression profiles to disease-free humans). (See Claim 1) The reference further teaches that the biological sample comprises peripheral human blood (would read on peripheral blood sample; See Claim 3, for example). In addition, the reference teaches that the cytokine interleukin-8 (IL-8) mRNAs is identified as being more abundant in the peripheral blood of patients with metastatic prostate cancer, which would read on (identifying) the one or more genes is differentially expressed in peripheral blood mononuclear cells (See Paragraph 472 of the reference). The reference teaches the biological sample could be a whole blood sample (see paragraph 287). The reference further teaches that the gene expression level is measured by RT-PCR and immunoassay (see Claims 9, 18, 14 and 15, for examples). The reference teaches the confirmation of tumor burden of the diseased individuals in relation to gene levels obtained from the peripheral blood samples (would refer to expression profile of the one or more genes in peripheral blood samples of patients having said solid tumor; See paragraph 469 of the reference). Furthermore, the reference teaches gene levels in patients with Stage D prostate cancer with metastatic tumors (would read on patients having two different tumors; See Paragraph 287 and Table 10).

Thus, the reference clearly anticipates the claimed invention.

8. Claims 1-6 and 16-18 are rejected under **35 U.S.C. 102(b)** as being anticipated by Olive et al (Immunology and Cell Biology. Vol. 76: 357-362. 1998).

The instant claims briefly recite a method comprising comparing gene expression profiles of one or more genes from peripheral blood cell samples (peripheral blood mononuclear cells) between patents with a solid tumor and disease-free humans. If the one or more genes consist of

only one gene, then it could not be IL1B, IL6, MMP-9 or FCGR3B. If the one or more genes consist of two genes, then the combination could not be IL1B and IL6. The solid tumor disease could be RCC (renal cell carcinomas), prostate cancer, OR head/neck cancer.

Olive et al teach a method for determining the expression of cytokine mRNA transcripts in peripheral blood by RT-PCR by using samples from both patients with RCC and normal individuals (See Abstract). The reference teaches harvesting peripheral blood mononuclear cells (would read on whole blood samples or blood samples enriched with PBMCs; See Page 358, right column, 1st paragraph). The reference also teaches comparing various gene transcripts between the peripheral blood samples of RCC patients and normal healthy donors (would read on comparing gene expression between samples from patients with solid tumor and disease-free humans; See page 360, Left column, 2nd paragraph). Furthermore, the reference teaches IL-10 and IFN-γ are differentially expressed between diseased and normal samples (would read on identifying or comparing genes that are differentially expressed; See page 360, Left column, 2nd paragraph).

Thus, the reference clearly anticipates the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-10 and 15-18 are rejected under 35 U.S.C. 103(a) as being obvious over Ralph et al (US 6,190,857 B1; 2/20/2001), in view of Golub et al (Science. Vol. 286: 531-527; 1999).

The instant claims briefly recite a method comprising comparing gene expression profiles of one or more genes from peripheral blood cell samples (peripheral blood mononuclear cells) between patents with a solid tumor and disease-free humans. If the one or more genes consist of only one gene, then it could not be IL1B, IL6, MMP-9 or FCGR3B. If the one or more genes consist of two genes, then the combination could not be IL1B and IL6. The solid tumor disease could be RCC (renal cell carcinomas), prostate cancer, OR head/neck cancer. In addition, the method also comprises using weighted voting and/or correlation metric algorithm.

Ralph et al teach diagnostic techniques for the detection of human disease states that affect gene expression in peripheral leukocytes as described supra.

Ralph et al do not specifically teach using the specific statistical analysis tool (such as weighted voting algorithm).

However, Golub et al teach cancer classification based on gene expression by using statistical analysis including weighted voting algorithm (See Abstract and Page 532, right column, first paragraph). The reference also teaches the advantages of using these statistical tools to analyzing gene expression profiles such as "class predictors can be constructed for known pathological categories-reflecting a tumor's cell of origin, stage, or grade. Such predictors could provide diagnostic confirmation or clarify unusual cases."

Therefore, it would have been prima facie obvious for an ordinary skilled artisan to generate a method comprising comparing gene expression profile of one or more genes from peripheral blood samples using known statistical tools to analyze the expression pattern. Due to

the advantages taught by Golub et al that is classification based on gene expression profile with weighted voting algorithm would be using in cancer diagnosis, a person of ordinary skill in the art would have been motivated at the time of the invention to use the statistical analysis taught by Golub et al to process gene expression profile data generated by comparing differential gene expression between diseased and normal humans. Since the statistical methods are known and are successful for comparing differential gene expression profile in cancer patients as taught by Golub et al, an ordinary skilled artisan would have reasonable expectation of success of achieving such modifications.

In conclusion, the invention of the instant claims would have been prima facie obvious over Ralph et al, in view of Golub et al to one of ordinary skill in the art without evidence to the contrary.

11. Claims 1, 2, 4-7, 9-13 and 16-18 are rejected under 35 U.S.C. **103(a)** as being obvious over Ralph et al (US 6,190,857 B1; 2/20/2001), in view of Liu et al (Infection and Immunity. Vol. 69: 2788-2796; 2001).

The instant claims briefly recite a method comprising comparing gene expression profiles of one or more genes from peripheral blood cell samples (peripheral blood mononuclear cells) between patents with a solid tumor and disease-free humans. If the one or more genes consist of only one gene, then it could not be IL1B, IL6, MMP-9 or FCGR3B. If the one or more genes consist of two genes, then the combination could not be IL1B and IL6. The solid tumor disease could be RCC (renal cell carcinomas), prostate cancer, OR head/neck cancer. The one or more gene is drawn to the TLR2 gene.

Ralph et al teach diagnostic techniques for the detection of human disease states that affect gene expression in peripheral leukocytes as described supra. In addition, the reference also teaches "Genes that were either up regulated or down regulated in blood from metastatic cancer patients were identified. One of the mRNAs identified as being more abundant in the peripheral blood of patients with metastatic prostate cancer was the cytokine interleukin-8 (IL-8). Hence, the immune system is an attractive choice to survey because it would be expected to respond robustly to a malignant disease process. As such, by examining the peripheral blood mononuclear cell population, evidence of cancer presence was obtained without requiring any knowledge of its physical location in the body." (See Paragraph [472] of the reference)

Ralph et al do not specifically teach using TLR2 gene in the method. The reference also does not specifically teach the blood sample is enriched with PBMCs.

However, Liu et al teach TLR2 is predominantly distributed in monocytes/macrophages (would refer to mononuclear cells; See page 2788, left column, 2nd paragraph). The reference also teaches that TLR2 is involved in the signal pathway of NF-κB of the immunosystem. The reference also teaches isolating monocytes (would read on PBMCs) by centrifugation from blood of healthy donors (See Page 2789, right column, 1st paragraph).

Therefore, it would have been prima facie obvious for an ordinary skilled artisan to generate a method comprising comparing gene expression profile of TLR2 gene from peripheral blood samples that is enriched with PBMCs from diseased and healthy humans. Since Ralph et al teach that immune system is an attractive choice to survey because it would be expected to respond robustly to a malignant disease process, and examining the peripheral blood mononuclear cell population would provide evidence of cancer presence without requiring any

knowledge of its physical location in the body, a person of ordinary skill in the art would have been motivated at the time of the invention to use compare differential gene expression profiles obtained from peripheral blood samples. Due to the fact that TLR2 is expressed in the PBMCs and is known to be involved in immune signal pathway as taught by Liu et al, an ordinary skilled artisan would motivated to compare TLR2 gene expression profile from samples obtained from diseased and healthy individuals. In addition, the sequence of TLR2 or TIL4 are known in the prior art as evidenced by the GenBank accession number (AF051152 or SEQ ID No1) recited in Table 4 of the instant specification. The TLR2 RNA transcript would hybridize under stringent condition to CPS No 1 (which consisting of the nucleotides 2325-2635 if SEQ ID No1) of Table 2, and hybridize to a qualifier (e.g. SEQ ID No. 340) recited in Attachment A. Therefore, an ordinary skilled artisan would have reasonable expectation of success of achieving such modifications of comparing gene expression profiles using sequences derived from TLR2 gene.

In conclusion, the invention of the instant claims would have been prima facie obvious over Ralph et al, in view of Liu et al to one of ordinary skill in the art without evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SL
Art Unit 1639
11/30/2005

PADMASHRI PONNALURI
PRIMARY EXAMINER